The first ligand-modulated oxidative Heck vinylation. Efficient catalysis with molecular oxygen as palladium(0) oxidant†

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The discovery of the first ligand-supported Pd(II) catalysed oxidative Heck reaction with molecular oxygen as reoxidant and the scope with diverse arylboronic acids and olefins using only 1–2% of catalyst are reported.

The transition metal (Pd, Rh, Ru and Ir)[1] catalysed cross-coupling of organoboronic acids and olefins is rapidly growing as a versatile synthetic methodology. The multifarious advantages of arylboronic acid over other arylpalladium precursors (triflates, halides, *etc.*) include 1) the availability of vast numbers of arylboronic acids, 2) the stability to air and moisture, 3) the low toxicity and 4) the easy removal of boron-derived byproducts unlike that of other organometalloids.[2] The Pd(II)-mediated vinylic substitution of organoboronic acids, known as the oxidative Heck reaction, was first reported by Heck[1] with stoichiometric amounts of Pd(II) more than two decades ago. However, this reaction has been developed very little, barring a few recent reports. The first catalytic protocol was reported by Cho *et al.* using AcOH as solvent[3a] followed by a mild method by Du *et al.* using DMF as solvent with Cu(OAc)$_2$ as reoxidant.[3b] We recently developed a microwave-accelerated procedure for the fast generation of oxidative Heck products,[3c] and Jung *et al.* reported the utility of molecular oxygen as an efficient reoxidant of Pd(0), though with relatively high amount of Pd(II) (10 mol%).[3d]
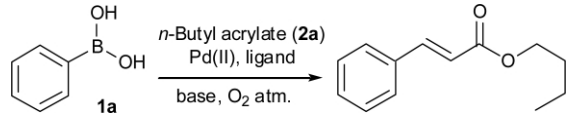
The complete absence of ligand-supported oxidative Heck protocols limits the development of selective and efficient applications in organic synthesis. The presence of ligands might not only invoke the stability of the catalyst by preventing the aggregation of Pd(0), prompting smaller amounts of catalyst, but also aid in control over the regio- and stereoselectivity with electron-rich and prochiral olefins respectively. In particular, the nitrogen ligands are known to facilitate the efficient reoxidation of Pd(0) by molecular oxygen.[4] In general, nitrogen-based ligands are very cheap, air and moisture stable compared to their phosphine counterparts. To start with, we undertook studies on the viability of ligands in the oxidative Heck reaction with more-common electron-poor olefins, which are reported herein.

A set of 19 optimisation experiments were performed to discover proper conditions in terms of Pd(II) source, solvent, ligand, base, temperature and time with PhB(OH)$_2$ (**1a**) and *n*-butyl acrylate (**2a**) as model reactants (Table 1). Molecular oxygen was used throughout as reoxidant for catalyst regeneration because of its eco-friendly advantages. The oxidatively stable phenanthroline-class ligand, 2,9-dimethyl-1,10-phenanthroline (dmphen), known to provide high yields in internal arylation with aryl triflates,[5] performed generally well. In contrast, the exclusion of the ligand did not afford any product (entry 18). Bipyridyl and monodentate pyridine[6] were ineffective (entries 14, 15). The phosphines, Ph$_3$P and BINAP, which are susceptible to oxidation,[7] gave moderate yields (entries 12, 13). The inferior yields with phosphine ligands

were due to the poor percentage of conversion and also the concurrent formation of biphenyl through the homocoupling of PhB(OH)$_2$, which was negligible with dmphen ligand. The nitrile solvents, MeCN and EtCN, gave the highest yields (entries 8–11). The polar, aprotic solvent DMSO afforded only poor to moderate yields, even after prolonged time (entries 4–6). Toluene gave a slightly depressed yield (entry 7). *N*-Methylmorpholine (NMM) was identified as an effective base and 2 equiv. proved to be optimal. Et$_3$N was also effective (entry 16), but the inorganic base LiOAc gave a poor result. While the acid **1a** readily coupled to the olefin, the corresponding boronic ester was surprisingly inert under the reaction conditions.

The immediate impact of the dmphen ligand-support was that the reaction could be performed with 1 mol% of Pd(II), down from 10 mol% in the absence of the ligand.[3d] Having identified an efficient catalytic system, we then investigated the scope of arylboronic and olefinic substitution. The results from preparative coupling of olefins (**2a–d**) with a diverse set of boronic acids, bearing sensitive nitro, keto, bromo, and iodo functionalities, (**1a–m**), are summarised in Table 2. The standard conditions identified from Table 1 (entry 11) were employed, even though individual cases were optimised for high yield, with regard to Pd(OAc)$_2$ amount (1 or 2 mol%), solvent and temperature. The reactions were diastereo- and regioselective, except that of the styrene derivative (last entry).

Table 1 Ligand-based optimisation of oxidative Heck protocol[a]

Entry	Solvent	Ligand [L/Pd]	Base	T/°C	t/h	Yield[b] (%)
1	DMSO	—	LiOAc	50	24	36
2	DMSO	—	LiOAc	70	24	0[c]
3	1,4-Dioxane	dmphen [1.0]	2,6-Lutidine	70	24	0[d]
4	DMSO	dmphen [1.0]	LiOAc	70	24	27
5	DMSO	dmphen [4.0]	LiOAc	70	30	25
6	DMSO	dmphen [1.0]	NMM	50	24	69
7	Toluene	dmphen [1.0]	NMM	80	12	78
8	EtCN	dmphen [1.2]	NMM	70	12	95
9	EtCN	dmphen [1.0]	NMM	50	12	97
10	MeCN	dmphen [1.2]	NMM	50	12	97
11	MeCN	dmphen [1.2]	NMM	50	6	96
12	MeCN	Ph$_3$P [2.5]	NMM	50	24	44
13	MeCN	BINAP [1.2]	NMM	50	24	47
14	MeCN	bipy [1.2]	NMM	50	24	0
15	MeCN	pyridine [4.0]	—	50	6	0
16	MeCN	dmphen [1.2]	Et$_3$N	50	12	90
17	MeCN	dmphen [1.2]	LiOAc	50	12	20
18	MeCN	—	NMM	50	12	0
19	MeCN	dmphen [1.2]	NMM	50	12	22[e]

[a] **1a** (2.0 mmol), **2a** (1.0 mmol), Pd(OAc)$_2$ (1 mol%), ligand (L) and base (2.0 mmol) in MeCN (2.5 mL) were stirred under O$_2$ atm. [b] Isolated yield with purity ≥95% (GC-MS). [c] Pd(II): Pd(phen)Cl$_2$. [d] Pd(II): Pd(MeCN)$_2$Cl$_2$. [e] Additive: LiBr (5 equiv.).

† Electronic Supplementary Information (ESI) available: Experimental and analytical data. See http://www.rsc.org/suppdata/cc/b3/b311492a/

Table 2 Vinylation of diverse arylboronic acids with olefins[a]

ArB(OH)₂ + ═─EWG → Ar─═─EWG

$ArB(OH)_2 + \!=\!\!-EWG \xrightarrow[\text{O}_2 \text{ atm., MeCN}]{\substack{\text{Pd(OAc)}_2, \\ \text{dmphen, NMM,}}} Ar\!-\!\!=\!\!-EWG$

1a-m   2a-d

R–PhB(OH)₂	Olefin[b]	Product[c]	Cond.	t/h	Yield[d] (%)
3,4-dioxy methylene **1b**	**2a**		A	6	95
4-methyl **1c**	**2a**		A	3	73
			B	6	92
4-methoxy **1d**	**2a**		A	6	70
3-nitro **1e**	**2a**		B	12	40
3-acetyl **1f**	**2b**		A	24	77
4-acetyl **1g**	**2a**		A	12	0
3-iodo **1h**	**2a**		A	12	43
				12	45[e]
3,5-dibromo **1i**	**2a**		B	12	67
3-bromo **1j**	**2c**		B	12	73
2,4,6-trimethyl **1k**	**2a**		B	12	43[f]
2-methoxy **1l**	**2a**		B	6	77[g]
1-naphthyl **1m**	**2c**		B	6	77
1a	**2d**		B	12	83[h]

[a] Condition **A**: ArB(OH)₂ (2.0 mmol), alkene (1.0 mmol), Pd(OAc)₂ (2.3 mg, 1 mol%), dmphen (2.6 mg, 1.2 mol%), and NMM (0.22 mL, 2.0 mmol) in MeCN (2.5 mL) were stirred under O₂ atm at 50 °C, except as noted; **B**: L/Pd(II): 2.4/2 mol%. [b] **2a**: n-Butyl acrylate; **2b**: styrene; **2c**: 1-octen-3-one; **2d**: 4-ethoxystyrene. [c] New compounds gave satisfactory ¹H and ¹³C NMR, IR, and combustion analysis. [d] Isolated yield with purity ≥95% (GC-MS or ¹H NMR). [e] L/Pd(II): 6.0/5.0 mol%. [f] Solvent: DMF, 100 °C. [g] Solvent: EtCN, 80 °C. [h] β : α = 83 : 17.

The general trend was that the electron-rich arylboronic acids were the superior substrates affording high yields without any byproduct. The m-substituted electron-poor arylboronic acids (**1e–f**, **1h–j**) afforded moderate to good yields, while those with p-substitution[8] were inert towards vinylation and only furnished homocoupling products in small amounts (e.g. **1g**). The fluoride salt additives like CsF and TBAF, which are known to generate highly-nucleophilic "ate" complexes with ArB(OH)₂, made no difference in the latter case.[9] This large disparity in the reactivity might indicate that the insertion of electron-poor aryl groups in a chelation-controlled cationic Pd(II) π-intermediate is a sluggish process. This is in contrast to ligand-free oxidative Heck conditions, where the π-complex might be neutral.[10,11] The addition of LiBr decelerated the reaction rate with non-functionalised **1a**, which supports the role of the cationic pathway (entry 19, Table 1).[12] The formation of the branched isomer (17%) in the last entry (Table 2) may also be interpreted based on the cationic mechanism. The sterically-hindered boronic acids, **1k–l**, gave moderate to good yields. The reactions with **1h-j** are highly chemoselective as no competitive Pd(0)-catalysed Heck vinylation and Suzuki coupling were noticed.

In conclusion, ligand modulated oxidative Heck chemistry was developed with 1) arylboronic acids as latent aryl halides, 2) low catalyst loading with an inexpensive ligand and 3) molecular oxygen as a "green reoxidant". This protocol should serve as the foundation for the future development of regio- and stereocon-trolled chemistry. Our further efforts are directed towards the above goal,[13] and overcoming limitations pertaining to the eletron-poor arylboronic acids.

Notes and references

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12 This is in agreement with the results obtained in internal vinylation of aryl triflates with dmphen as ligand. See ref. 5.
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